April 3, 2003

Timothy Adams, Ph.D.
Technical Contact
The Flavor and Fragrance High Production Volume Consortia
The Terpene Consortium
1620 I. Street, N.W.
Suite 925
Washington, DC 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Anethole posted on the ChemRTK HPV Challenge Program Web site on December 4, 2002. I commend The Flavor and Fragrance High Production Volume Consortia's Terpene Consortium, for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Flavor and Fragrance High Production Volume Consortia, The Terpene Consortium advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Anethole (isomer unspecified) and *trans*-Anethole

SUMMARY OF EPA COMMENTS

The sponsor, the Terpene Consortium of the Flavor and Fragrances High Production Chemical Consortia, submitted a test plan and robust summaries to EPA for anethole (isomer unspecified) and *trans*-anethole (CAS Nos. 104-46-1 and 4180-23-8, respectively) dated November 12, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 4, 2002.

1. Physicochemical Properties. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

2. Environmental Fate. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. Additional information is needed in the robust summaries.

3. Health Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

4. Ecological Effects. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program. Additional information is needed in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE ANETHOLE (ISOMER UNSPECIFIED) AND *trans*-ANETHOLE CHALLENGE SUBMISSION

General

The test plan covers two substances: *trans*-anethole, and anethole (isomer unspecified) which contains predominantly the *trans* isomer (greater than 85% when produced industrially). Because of the close structural relationship between the isomers and the similar toxic responses observed in a number of tests, only small differences in toxicity are expected for these isomers.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Stability in water. While the test plan correctly states that anethole does not hydrolyze, the submitter needs to provide this reasoning in the robust summary.

Transport and distribution (fugacity). The data provided by the submitter are adequate for the purposes of the HPV Challenge Program; however, the submitter needs to include in the robust summary the input values to the model.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

All SIDS-level endpoints for anethole and *trans*-anethole have been adequately addressed for the purposes of the HPV Challenge Program. Although there are problems with certain aspects of individual studies and missing details, the data are acceptable on a weight-of-evidence basis for acute toxicity, repeated-dose toxicity, genetic toxicity and reproductive/developmental toxicity.

Ecological Effects (fish, invertebrates, and algae).

The data referenced by the submitter are adequate; however, the submitter did not include critical information in the robust summaries. Although EPA has made a determination by examining the studies, the submitter needs to incorporate the missing details.

Specific Comments on the Robust Summaries

General

The purity of the test substance was not included in many of the robust summaries.

Health Effects

Acute Toxicity. Of seventeen studies submitted, omissions included: the identification of the vehicle used, the administered doses, mortality results by dose, information on clinical signs and symptoms other than death and the method for calculating the LD_{50}.

Repeated-Dose Toxicity. The summary of a 177-week assay in rats on *trans*-anethole omitted the specific hematological parameters assessed, the organs examined for histopathology, and the mortality results by dose and sex. In addition, details concerning clinical chemistry were not reported.

Genetic Toxicity. There are a number of omissions such as the criteria for scoring the results, the number of replicates, and the cytotoxic concentrations for the Ames assays. For a bone marrow micronucleus test, omissions included the group sizes and the number of cells examined per dose.

Reproductive Toxicity. A robust summary for a pre-guideline 4-generation reproductive toxicity test in rats exposed to *trans*-anethole in the diet did not specify the numbers of males and females that were caged together during mating or the group sizes (numbers of pregnant females) for each generation. The reported methods were consistent with OECD Guideline 416 (2-generation study) except that a single dose was administered.

Developmental Toxicity. The robust summary identifies the test substance as anethole (isomer unspecified), while a published reference on p 807 identifies the test material as *trans*-anethole (Newberne, et al.). The submitter needs to resolve the discrepancy.

Ecological Effects

Fish. The submitter needs to include information on the electronic diluter used to minimize evaporation losses, flow rate, the number and volume of additions per day, the treatment concentrations used and the number of replicate tests.

Invertebrates. The submitter needs to include information on the electronic diluter used to minimize evaporation losses, flow rate, the number and volume of additions per day, the treatment concentrations used and the number of replicate tests.

Algae. The submitter needs to include pH, water temperature, water hardness, chemical purity, and information on the type and frequency of analytic measurements used to determine the concentration of the test chemical.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

Reference

Newberne, et al.,1999. The FEMA GRAS Assessment of trans-Anethole Used as a Flavouring Substance, Food and Chemical Toxicology 37:789-811.